great majority had no difficulty in understanding and carrying out the method, and they kept their appointments and their charts very well. Though numerous patients missed occasional tablets, the majority of tablets were taken regularly and conscientiously. The routine of pill-taking became automatic. As one patient remarked, "the beauty of the pill is that you can forget it."

However, it must be realized that the women in the trial were selected in that, for various reasons, they did not favour mechanical contraception. Therefore it was to be expected that they would be favourably inclined towards an entirely different method of birth control. Also the tablets, supplied by G. D. Searle & Co. Ltd., were issued free to the patients.

Numerous cases of marital difficulties were encountered, and in some, no doubt, these problems prompted the patients to enter the trial. Most were improved as a result of so doing, but many more complex factors must have been involved than the mere taking of a pill. The overall effect, however, was that the patients felt an increase in well-being and marital happiness. The effects were not limited to the wives. Many husbands expressed their satisfaction with the method and none wished to return to methods formerly used. One man was almost impotent and returned to full potency, but it would be unwise to draw conclusions from a single case.

None of the marital problems became worse, but in those cases where there was no improvement there was a deepening sense of disappointment. It remains to be seen whether these patients will eventually give up oral contraception. To date, they have chosen to continue, despite the fact that it is not the panacea for their marital ills as they anticipated.

Those patients who had left the trial to become pregnant conceived in the cycle following the cessation of tablets. One patient miscarried at eight weeks, and one pregnancy continues normally. The third patient had a normal quick delivery of a healthy 8¼-lb. (3.8-kg.) girl, and this was followed by an abundant lactation.

The minor disadvantages of oral contraceptives can readily be shown by tables. The contribution they make to human happiness does not lend itself to statistical analysis. The overall clinical impression is that conovid-E is psychologically and physically acceptable and its effects are reliably reversible over the time tested.

Summary

The object of the trial was to ascertain the smallest dose of norethynodrel combined with ethinyloestradiol-3-methyl ether that would be an efficient contraceptive.

After 17 months 162 women out of the first 200 fertile volunteers were still in the trial and information has been obtained from 1,114 woman-months of therapy.

The routine administration of 21 tablets, followed by seven days without tablets, is acceptable to the patients.

Menstrual-cycle control on a tablet of 2.5 mg. of norethynodrel with 0.1-mg. of ethinyloestradiol-3-methyl ether was unsatisfactory in 30% of women, but "spotting" and breakthrough bleeding were checked by increasing the dosage to one and a half tablets.

Nausea was the side-effect most often complained of, but this was limited to the first three cycles.

No pregnancies occurred when the tablets were taken as prescribed.

After cessation of the treatment, ovulation and fertility appeared to be unimpaired.

The trial continues.

It is concluded that a tablet of 2.5 mg. of norethynodrel with 0.1 mg. ethinyloestradiol-3-methyl ether gives full effective conception control. The patients were strongly in favour of oral contraception once they had used this method of birth control.

Dr. E. Mears and Dr. G. R. Venning have given great help in the organization of the trial (first run by Dr. G. Newbury) and in the preparation of this paper. Dr. A. Wiseman has willingly supplied additional data. The clerical work was ably carried out by Mrs. Anne Try. The trial would not have been possible without the willing co-operation of the volunteers.

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DETERMINING THE CLIMATIC LIMITATIONS OF A CHILDREN'S CANCER COMMON IN AFRICA

BY

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It has recently been recognized that a strikingly characteristic lymphoma syndrome is the commonest children's cancer across tropical Africa. The clinical and pathological features of the varying manifestations of this multifocal neoplasm have been described elsewhere (Burkitt, 1958, 1962a, 1962b; O'Conor and Davies, 1960; Burkitt and O'Conor, 1961; O'Conor, 1961; Burkitt and Davies, 1961).

One of the most fascinating aspects of this easily recognizable syndrome is its limited geographical distribution. The rough outline of the tumour-bearing belt across Africa (Fig. 1) has been described in the papers referred to above, and its obvious relationship to certain climatic factors has been stressed. Moreover, the marked similarity between tumour distribution and tsetse infestation has been noted.

Recently extensive travel has been undertaken to determine more accurately the limits of this "tumour belt" and the physical and climatic conditions determining the boundaries. These journeys have been made in order to provide what might well be termed "geographical biopsies"—that is, detailed surveys of portions of Africa containing "tumour-bearing" and "tumour-free" areas, analogous to the surgeon's biopsy in which the pathologist expects to find the change from normal to diseased tissue.

Tumour "Safaris"

In the past this East African term applied primarily to foot travel with porters. It is now used for journeys by almost any means, usually of more than a day's duration.

Three surveys of this nature have been carried out during the nine months October, 1961, to June, 1962. The " biopsy " site was chosen with care. The northern limits of the " tumour belt " were discarded in view of the fact that population densities fall off as desert conditions are approached. This would inevitably result in the disappearance of tumour. The southern limit of West Africa, being the sea-coast, was inevitably rejected, and further east the centre of Angola was neither

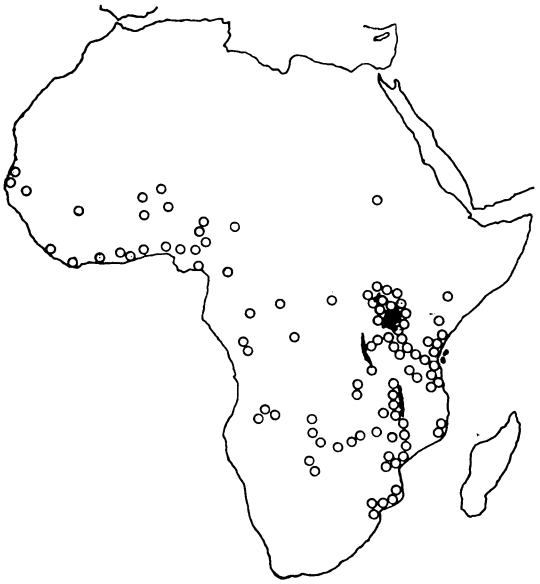

FIG. 1.—Known tumour distribution in Africa.

inviting nor promising of results. There remained the southern edge of the eastern end of the " belt " with its coastal tail.

Before starting the first safari, the longest in time and distance travelled, an altitude barrier to tumour occurrence had been demonstrated in Uganda and the adjoining part of Kenya. It appeared that near the Equator the tumour could be expected to occur anywhere except at altitudes above about 5,000 ft. (1,524 m.).

East, South, and Central Africa

After prolonged postal preparation to alert doctors to be watchful for these lesions, a 10,000-mile (16,090-km.) road safari was undertaken together with two colleagues, Dr. Ted Williams and Dr. Clifton Nelson. Over 50 hospitals were visited, and information was obtained from many more through doctors who had served in several stations. The strikingly characteristic jaw tumours, which cannot easily be mistaken for any other condition, were used as an index to the existence or absence of the syndrome in any area. Particulars of this survey have been published (Burkitt, 1962c, 1962d).

In brief, the significant findings were as follows: As the distance from the Equator increased, so the tumour altitude barrier progressively fell (Fig. 2). Thus in the Rhodesias and Nyasaland it was limited to the great river valleys and the shores of Lake Nyasa. It was found to occur throughout the coastal plain of Mozambique. At the latitude in which the southern tip of this country lies it has been recognized only on this coastal strip with a few exceptions that can probably be explained on a basis of migration. In view of the relation between altitude barrier and latitude, the actual operative factor was deemed to be minimum temperature, the critical level being around 60° F. (15.5° C.) (Fig. 3).

Ruanda-Urundi

It had originally been intended to include this country in the previous safari, but unprecedented weather conditions had rendered roads of access completely impassable. A survey there was considered of crucial importance and considerable urgency. This is the most densely populated country in Central or East

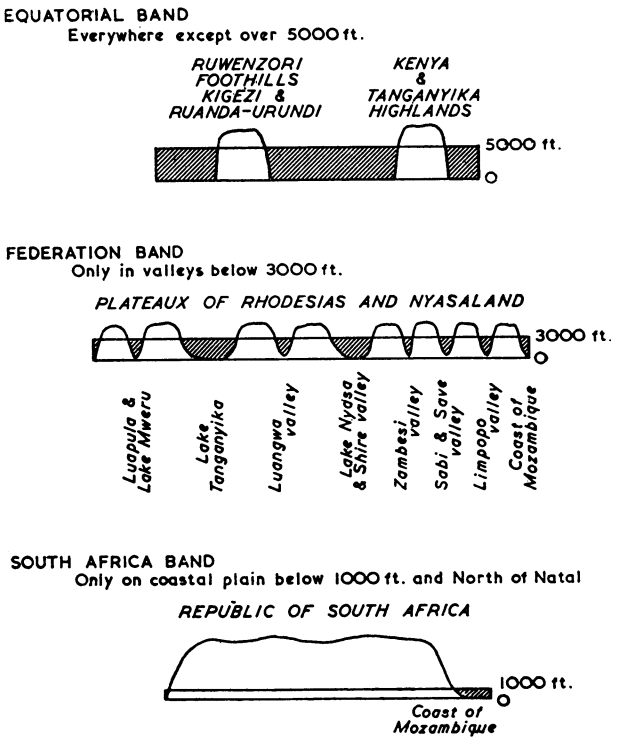

FIG. 2.—Diagrammatic representation of decreasing altitude barrier with increasing distance from the Equator. Shading indicates areas of potential occurrence of tumour.

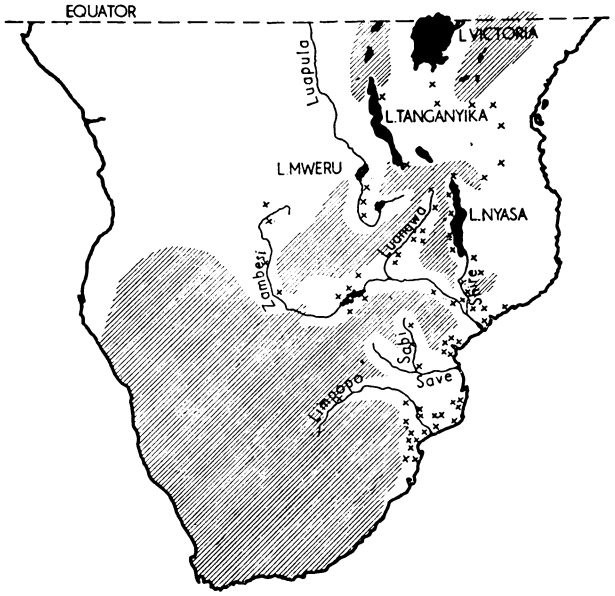

FIG. 3.—Subequatorial Africa. Only in the shaded areas do temperatures fall below 64° F. (17.8° C.). The crosses indicate places where the tumour syndrome has been recognized.

Africa. It lies just south of the Equator, but low temperatures are recorded, as most of the territory is at an altitude over 5,000 ft. (1,524 m.) above sea-level (Fig. 4). The occasional low areas are thinly populated. The urgency was imposed by the threatened exodus of many doctors, all of whom were expatriates, owing to the expectation of almost immediate independence. The departure of most trained medical observers with their fund of experience would have made an inquiry of the nature proposed almost valueless.

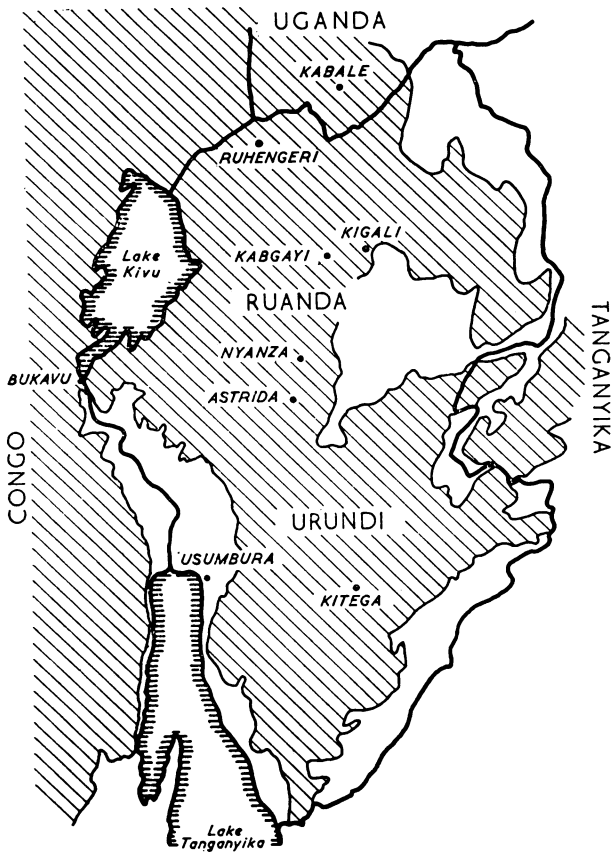

FIG. 4.—Ruanda-Urundi. All shaded areas are over 5,000 ft. (1,524 m.) above sea-level. Much of the remainder is sparsely populated swamp or game park.

The East African Medical and Research Foundation kindly put their aircraft and pilot at my disposal. This enabled a survey to be done in three days which otherwise might have occupied ten.

Findings

Usumbura, the capital, stands on the north-east shore of Lake Tanganyika, at an altitude of 2,500 ft. (762 m.) above sea-level. The plain around the town has only recently become inhabited, and over 90% of hospital admissions still come from the hills to the north and east. The tumour syndrome being investigated was described to virtually all the medical staff with the aid of an album of photographs depicting every aspect of this condition. Although some had recognized these characteristic lesions during previous service in the Congo, only one doctor could remember having seen a case in Ruanda-Urundi—a boy with a mandibular tumour seen at Usumbura. A search through hospital and laboratory records for five years did not produce evidence of a single case.

Astrida and Kigali were then visited, and staff with long experience were quite convinced that these jaw lesions had never been seen at these centres. Senior doctors with experience up to 25 years at Kabgayi and Kitega were also interviewed, and they voiced an identical experience.

The same negative information was forthcoming from a number of senior doctors working in mission hospitals scattered throughout the country.

With the single exception of the one patient remembered at Usumbura, no evidence suggesting the existence of this tumour was obtained from any medically qualified observer. Two medical assistants thought they had each seen a child with a lesion resembling the pictures they were shown.

This evidence has since been corroborated by P. L. Gigase (personal communication, 1962), who had access to pathological investigations carried out on tumours from eight medical centres in Ruanda-Urundi and two in the topographically similar country of Eastern Kivu. The Ruanda-Urundi hospitals had supplied material from over a thousand cancer patients. Eighty-eight were children, but no single case of lymphoma was recorded.

Of 42 children's cancers seen during a seven-year period at Katana, in Kivu, there were four lymphomas diagnosed histologically, but none of these conformed to the particular syndrome. Moreover, a report of neoplasms observed in the E.N.T. department at Usumbura during the years 1956–8 by Marneffe (1958) reveals only one case likely to have been one of these tumours.

It can thus be concluded that the condition is virtually unknown throughout the hilly though densely populated country of Ruanda-Urundi. In striking contrast it is so prevalent south of Lake Victoria, less than 200 miles (320 km.) to the east, and at an altitude of 4,000 ft. (1,220 m.), that the staff at a 70-bed mission hospital have seen one or two cases every month.

The experience in Ruanda-Urundi is exactly parallel to the experience in the adjacent south-west part of Uganda, which is topographically identical. In spite of the fact that it is the most densely populated region in Uganda, it is the only district from which no single patient with this syndrome has been recorded.

West Africa

East and Central Africa, with extremes of altitude within a limited compass, proved eminently suited for studying the effect of altitude, and therefore of temperature, on tumour distribution.

West Africa, in contrast, is relatively flat. The only areas in Nigeria lying above 3,000 ft. (914 m.) are the Bukuru Plateau and the extreme east bordering Cameroon. All of Ghana is less than 3,000 ft. (914 m.) above sea-level and most of it is below 1,200 ft. (365 m.).

Vast differences in humidity and vegetation are, however, observed. Rainfall varies from under 20 to over 400 in. (50 to 1,016 cm.) a year, and equatorial forest in the south contrasts with arid desert in the extreme north.

Nigeria

All three regions were visited. There is ample evidence that the tumour is common throughout the western region, and, although less information is

available for the east, the condition certainly exists in widely scattered areas.

The northern region provided one of the "geographical biopsies" alluded to above. Kano, in the far north, registers an annual rainfall of only 30 in. (76 cm.) (Fig. 5). Most of this, moreover, falls in the months of June, July, and August. Throughout the remaining nine months almost desert conditions prevail. Approximately three million people, equal to half the total population of Uganda, or more than the whole population of Nyasaland or Northern Rhodesia, live within a 30-mile (48-km.) radius of the city. Yet the tumour appears to be virtually non-existent. Competent observers had recognized no case in up to ten years' experience. The dental surgeon had recognized but one, from an eastern region tribe, and one general surgeon had seen "a few" in seven years. Kano is a large metropolis and these occasional cases may have been immigrant. The city and its environs could thus be considered virtually tumour-free. This territory constituted the healthy portion of a "biopsy" which entered a lymphoma area less than 150 miles (240 km.) to the south.

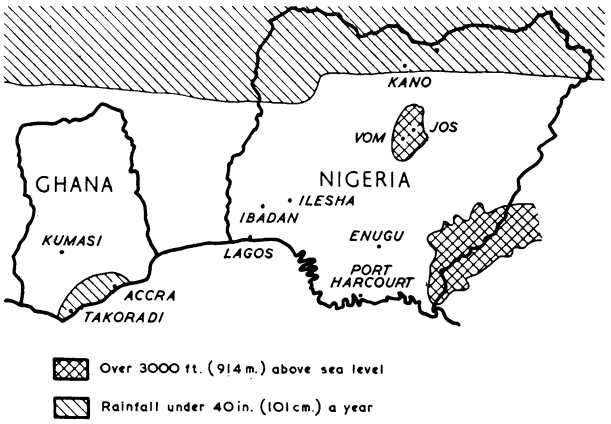

FIG. 5.—Nigeria and Ghana showing (1) areas where the rainfall is below 40 in. (101 cm.) a year and (2) areas at an altitude of over 3,000 ft. (914 m.) above sea-level.

The Bukuru Plateau commences some 100 miles (160 km.) south of Kano, and covers an area about 70 miles (112 km.) long and 40 miles (64 km.) wide. The population density on the plateau and in the surrounding country is only about one-sixth of that recorded round Kano. Jos is near the northern part of this plateau and contains the Central Government Hospital, at which one or two children with these jaw sarcomas are seen each year. There was no evidence to show whether these patients came from the plateau or from the plains to the east. Vom is on the south-west rim and most of the patients treated by the Sudan United Mission Hospital there come from the plains. The staff see some six to eight of these patients a year, and one was in the wards at the time of my visit.

The annual rainfall on the plateau is over 60 in. (152 cm.), and in the surrounding plains it is 50–60 in. (127–152 cm.) (Fig. 5). This is double that of Kano, and, moreover, is more evenly distributed through the year. Much of the plateau is agricultural country, and this, together with extensive tin-mining, has denuded most of the area of trees. The surrounding country is the merging area between Guinea and North Guinea vegetation, whereas the latter is giving place to Sudan vegetation around Kano. Church (1960) points out that the Nigerian Sudan, which includes Kano, stands in strong contrast to the middle belt in climate and vegetation.

It is suggested that the comparatively frequent occurrence of the tumour in the neighbourhood of Vom, and its definite recognition at Jos, compared with its virtual absence round much more densely populated Kano, results from differences in humidity and vegetation.

Ghana

Only the southern half of Ghana was visited, but experience there reflected Nigeria in reverse. Although the tumour definitely occurs in Accra, the incidence seems low, perhaps one or two cases seen each year at Korle Bu Hospital. At Kumasi, however, 170 miles (273 km.) north, the condition was universally recognized, and doctors who had worked in both centres were unanimous that it was very much commoner in Kumasi. Estimates of its frequency averaged six to eight admissions a year. Accra serves a slightly larger population.

Kumasi, with an annual rainfall of 54 in. (137 cm.), is surrounded by forest. Accra, on the other hand, is surprisingly dry, with an annual rainfall of only 27 in. (68.5 cm.) (Fig. 5). Unlike the luxuriant foliage of Southern Nigeria, the vegetation around Accra is mainly grass and stunted bush. Referring to this area, Church (1960) remarked that "the relative dryness and sparse vegetation were added attractions for the early European traders in gold and slaves."

Here again it is suggested that humidity, reflected by vegetation, has a bearing on tumour incidence. All of Ghana lies further south than Kano, and available evidence suggests that tumour cases have been observed in all the main medical centres.

Summary and Conclusions

A characteristic and unusual lymphoma syndrome is now recognized to be the commonest children's cancer in tropical Africa. The findings of three safaris undertaken to determine the factors responsible for the geographical limitations of the tumour are described.

Field surveys in East and Central Africa provided evidence that this tumour syndrome is altitude-dependent because temperature-dependent. Experience from West Africa suggests that it is humidity-dependent because vegetation-dependent.

The possibility that this tumour is vector-transmitted and may therefore be virus-induced has already been suggested. The observations recorded above would appear to strengthen this argument.

I gratefully acknowledge financial assistance from both the Medical Research Council and the Department of Technical Co-operation, London, which made these journeys possible. My thanks are also due to the Chief Medical Officer, Ministry of Health, Uganda, for freeing me from routine duties in order to undertake these investigations. Had not Professor I. W. J. McAdam, Head of the Department of Surgery, and my other surgical colleagues, willingly accepted additional commitments during my absence, this work could not have been done. King David's injunction, recorded in I Samuel xxx. 24, decreed that "as his part is that goeth down to the battle, so shall his part be that tarrieth by the stuff: they shall part alike." I trust that the same will apply in recognizing the contribution of my colleagues who "tarrieth by the stuff" to enable me to go

on safari. Finally, so many medical officers, specialists, and administrators in every country visited gave unstinting assistance and co-operation that mention of any names would be invidious. To one and all I offer my sincere thanks.

Figs. 1, 4, and 5 were produced in the Department of Medical Illustration in Makerere University College Medical School: Figs. 2 and 3 were produced by Dr. E. H. Williams, a companion in the road safari, and have been included by permission of the Editor of the *British Journal of Cancer.*

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RHEUMATIC FEVER AND THE BLOOD GROUPS*

BY

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J. E. AUER

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There is general agreement that group A haemolytic streptococcal infections of the upper respiratory tract are causally related to rheumatic fever. It is not understood why a few individuals develop rheumatic fever following such throat infections while most do not. This important question, the subject of many investigations most of which have been from an immunological point of view, remains without a satisfactory answer.

There is evidence to suggest that the presence of the mucopolysaccharide blood-group substances in saliva is related to susceptibility to rheumatic fever (Glynn and Holborow, 1961). These authors have suggested (Glynn and Holborow, 1952) that streptococci possibly convert blood-group substances to antigens which might then participate in the pathogenesis of rheumatic fever.

The evidence suggesting an association between the ABO blood groups and rheumatic fever is not as strong as that for the association to ABO (H) secretion. If there is a blood-group association, it could (*a*) simply reflect the "effect" of a blood-group substance being secreted in the saliva as suggested above, or (*b*) it might reflect a more general "effect" of gene action on enzymatic activity and cellular metabolism.

In this report the present status of our studies dealing with the possible association of the blood groups to rheumatic fever is described. The previously reported data suggesting an ABO-blood-group association for rheumatic fever are included (Buckwalter *et al.*, 1958). The findings of the ABO, rhesus, and MN blood groups, of the ABO (H) saliva secretion, and of the sibship studies are reported. The results obtained when our data are combined with those of other investigators and statistically evaluated are included in this communication. Finally, a working hypothesis is formulated on the basis of data recorded and discussed in this report.

Materials and Methods

All our data have been obtained from patients seen at the University of Iowa Hospitals during the past 15 years. The diagnoses have been established on clinical grounds or on the basis of operative findings. Blood and saliva samples were obtained from the patients and blood samples from their siblings. The standard-titre group-specific antisera used to type the blood were: A, B, absorbed anti-A, Rh_o, rh′, rh″, hr′, M, N, and anti-human. The techniques employed were those recommended by the supplier of the antisera. It is relevant to the results and important to point out that all the blood typings were performed by the same technician. An isohaemagglutination test, using anti-A and B sera and anti-O (H) in the form of a mixture made from ground *Ulex europaeus* seeds and 0.9% NaCl, was employed to determine the presence of blood-group substances in the saliva specimens.

Several different kinds of controls were used in ascertaining the statistical significance of the patient data. The 49,979 blood donors described in detail in a previous communication (Buckwalter and Knowler, 1958) were used to assess the total ABO findings (controls I). To evaluate the ABO subgroup (A_1, A_2, A_1B, A_2B), rhesus and MN blood groups, and saliva-secretion data a random sample of physicians, students, technicians, spouses of the patients, and patients with diagnoses other than those being studied were used as controls (II). Unaffected siblings of the patients provided a third set of controls (III). In another communication the reasons for using unaffected siblings as controls for blood-group disease studies have been discussed (Buckwalter *et al.*, 1960).

A modification of the method described by Woolf (1955) has been used to arrive at the statistical significance of the data. This method evaluates the significance of the differences in the incidence of the disease in the patients of the different blood groups. The incidences are determined from the blood-type frequencies observed in the patients and the controls. This is a more direct and natural way to think of the blood-group association than in terms of an increase or decrease in the patients' blood-group frequencies compared with control blood-group frequencies. This method has the added advantage of making it possible to combine and analyse data collected by independent investigators. The use of two programmes which have been written for the IBM 7070 digital computer by Dr. Edwards greatly facilitates the statistical analysis of the data. The results obtained when the data are examined by the conventional χ^2 method are given in another communication (Buckwalter and Tweed, 1962). A method devised by C. A. Smith, as described by Clarke *et al.* (1956), was used in determining the statistical significance of the sibling data.

*These researches were made possible by grants RG-4777 and A-3778 from the National Institutes of Health.